

## GUIDELINES

## Chapter 2-8. Anaerobic infections (individual fields): infections in the field of orthopedics (primarily bone and joint infections)

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### Introduction

Bones and joints, i.e. the focus of the field of orthopedics, are basically aseptic tissues. The distribution of administered antimicrobial agents in these tissues is lower than in other organs, often making it impossible to cure infections of bones and joints with antibiotics alone. In most cases with bone and/or joint infections, antimicrobial agents must be combined with surgical therapy. Gas gangrene and fasciitis are also anaerobic infections seen in the field of orthopedics, but these two conditions are discussed in another section. This section focuses on osteomyelitis and arthritis.

### Anaerobic osteomyelitis

#### Pathogenesis

Anaerobic infections affecting the bone frequently develop after open fractures, infection secondary to anaerobic infection of other organs, and foot osteomyelitis associated with angiopathy or diabetes mellitus. Because the unique structure of bone tissue makes it difficult for inflammatory cells to gather in the infected area and bacteria are likely to form a biofilm in the infected area, osteomyelitis tends to assume the form of a chronic rather than an acute disease.

#### Causative bacteria

*Staphylococcus aureus* and *Staphylococcus epidermidis* are generally responsible for osteomyelitis. Because of the recent increase in the number of patients using adrenocortical steroids or immunosuppressant drugs and in the

number of diabetic patients, the prevalence of anaerobic infection has been rising. Anaerobes often isolated from patients with osteomyelitis are anaerobic gram-positive cocci (*Peptostreptococcus* spp., *Finegoldia magna*, *Parvimonas micra*, etc.), *Bacteroides* spp. and *Clostridium* spp. Among others, *B. fragilis* is isolated particularly frequently. Osteomyelitis frequently assumes the form of a mixed infection of anaerobes plus aerobes rather than infection with anaerobes alone.

#### Diagnosis

Malodorous pus or the presence of a deep abscess or necrotic tissue is a possible sign of anaerobic infection, indicating the necessity of anaerobic culture. Gas pooling revealed by X-ray is an important finding, but it is important to notice that gas pooling is sometimes absent in anaerobic infection cases and can even be seen even in cases with aerobic infections.

#### Antimicrobial therapy

In cases strongly suspected of having an anaerobic infection, it is advisable to perform drip infusion of tazobactam/piperacillin (TAZ/PIPC), sulbactam/ampicillin (SBT/ABPC) or carbapenems (imipenem/cilastatin (IPM/CS), panipenem/betamipron (PAPM/BP), etc.). In cases in which the pathogen has been identified by culture, benzylpenicillin (PCG), piperacillin (PIPC), etc. should be selected for infections caused by anaerobic gram-positive cocci belonging to *Peptostreptococcus* spp., *Finegoldia* spp., *Micromonas* spp., etc. Most bacteria of *Bacteroides* spp. produce  $\beta$ -lactamase. Clindamycin (CLDM) is often used for such cases. Other than this drug, cephamycins

(cefmetazole (CMZ), etc.) and carbapenems (imipenem/cilastatin, etc.) are also expected to be effective. Aminoglycosides are ineffective against anaerobes [1].

Antibacterial agents are usually administered intravenously. In osteomyelitis cases, the distribution of administered antimicrobial agents in the infected focus is often low because necrotic bone or necrotic surrounding tissue hampers this distribution. Usually, the distribution of agents in bone marrow is about 1/10 of that in blood [2]. It is therefore desirable that administration of the drug at a dose allowing its blood concentration to reach a level equivalent to 10 times the MIC (minimal inhibitory concentration) of the agent against the pathogen. To achieve satisfactory efficacy, therapy with antimicrobial agents often need to be continued for 4–6 weeks, but there is no uniform criterion for the duration of treatment. Responses to antimicrobial chemotherapy are assessed on the basis of changes in clinical symptoms, white blood cell (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), etc. In chronically infected cases, intravenous antimicrobial chemotherapy is sometimes switched to oral treatment with antimicrobial agents effective against anaerobes [3]. Because suppurative osteomyelitis is likely to relapse and long-term careful follow-up is essential, the timing of antimicrobial agent discontinuation should be determined paying close attention to the indicators listed above.

### Surgical treatment

The presence of sequestrum or necrotic tissue can lead to expansion of the lesion and prolonged treatment. Adequate curettage of the affected area is therefore essential. If adequately treated, the duration of antimicrobial chemotherapy can be shortened. The most important surgical manipulations are thorough debridement (including removal of sequestrum, necrotic tissue, etc.), jet lavage with massive amounts of physiological saline, and drainage. Inadequate surgical manipulations can prolong the treatment period.

### Closed continuous lavage

An infusion tube and a discharge tube are inserted into the bone marrow. A cleanser, containing antimicrobial agents, is then infused through the infusion tube to guide necrotic tissue and bacteria out of the body via the discharge tube. Kawashima et al. devised a circuit for prevention of obstruction, employing a double-lumen serum tube and this circuit has been widely used [4]. Lavage is usually started with an initial volume of 5,000 mL and is continued with a maintenance volume of 3,000 mL per day.

### *Filling with cement beads containing antimicrobial agents (spacer) [5]*

This method uses bone cement (polymethylmethacrylate) containing antimicrobial agents to which the pathogen is susceptible. The aims are to fill dead spaces and maintain supra-effective local concentration of antimicrobial agent, with the ultimate goal of eradicating the bacteria. With this method, the local concentration of antimicrobial agent can be kept above that needed to be effective for about 2 weeks [6]. In cases of infection after hip replacement surgery, a spacer is often used after prosthesis removal. It is also used for prevention of bone shortening before planned reconstruction and for preservation of the patient's activity.

### *Oxygen under high pressure (OHP) therapy*

With hyperbaric oxygen therapy, arterial oxygen tension is elevated, and the resulting rise in dissolved oxygen in blood provides high concentrations of oxygen to tissues. This therapy suppresses *Clostridium* spp. proliferation and alleviates local ischemic condition. Although some investigators have described this therapy as being ineffective against non-*Clostridium* spp. infection [7], it is known to stimulate tissue repair and enhance neutrophil function. It is also reportedly effective against aerobes. OHP therapy therefore seems to be useful when combined with other treatment strategies.

## Anaerobic arthritis

### Pathogenesis

Arthritis caused by anaerobes is either an outcome of blood-borne transmission of bacteria from other tissues into joints or of direct bacterial invasion of the joints due to trauma, surgery, injection, etc. If articular cartilage is destroyed by inflammation or the like associated with infection, articular function is likely to be disturbed.

### Causative bacteria

Anaerobic arthritis accounts for about 1% of all cases of bacterial arthritis. It is most frequently attributable to *B. fragilis*. *Clostridium* spp. is rarely responsible for this infection [8].

### Diagnosis

Clinical symptoms of this infection are fever, local swelling, erythema and a sensation of heat. The range of motion (ROM) is restricted by pain. Care is needed because

patients with this infection sometimes show no typical local signs, complaining only of pain, and gradually develop articular destruction. If patients with a history of systemic or intra-articular administration of adrenocortical steroids show persistent pain or articular edema, the possibility of infectious arthritis (including anaerobic infection) should be kept in mind. A definitive diagnosis of this infection is possible if culture of the synovial fluid reveals anaerobes. However, some cases with this infection have negative anaerobic culture results. As in osteomyelitis cases, it is not uncommon for patients with anaerobic infection to show no signs of gas pooling in joints or subcutaneous tissues when examined by diagnostic imaging. Usually, there are no radiographic signs in the early stages of infectious arthritis. However, if infection persists, bone atrophy and articular destruction manifest in the surrounding area [9].

#### Selection of antimicrobial agents and how to use them

Like osteomyelitis, anaerobic arthritis is treated by drip infusion of TAZ/PIPC, SBT/ABPC, carbapenems (IPM/CS, PAMP/BP, etc.) or CLDM. Treatment is continued for about 2–4 weeks, with monitoring of changes in local signs, WBC, CRP, ESR, etc. Oral agents effective against anaerobes are administered, as needed, for about 2 months.

The most important aspect of treating infectious arthritis is preserving the articular cartilage. It is essential to minimize the degree of pain and articular dysfunction (including restricted ROM). Because lysis of cartilaginous proteoglycan begins 24 h after bacterial invasion of joints, the administration of treatment therapy must be started urgently. It is clinically advisable for antimicrobial agents to be administered immediately, followed by continuous lavage, if suppurative arthritis is suspected. Cleansing with

an injector does not consistently allow adequate drainage or cleansing and involves a risk of secondary infection. It is desirable that synovectomy be performed under arthroscopic guidance, and that this be followed by adequate cleansing and closed continuous lavage. It is difficult to manage suppurative arthritis with conservative therapy. Rapid and appropriate treatment by specialists is essential.

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